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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,767	05/27/1999	NICK GIANNOUKAKIS	A32362	5337

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/320,767	GIANNOUKAKIS ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/7/04 has been entered. Claims 31, 35 and 39 are currently pending and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 35 both recite the phrase, "transplanting the β cell of **step (a)**" (emphasis added; see step (ii) in each claim). However, claims 31 and 35 do not comprise a "step (a)". Therefore, the instant claims are indefinite as it is unclear which β cells are to be transplanted.

It is noted that amending the claims to recite "step (i)" instead of "step (a)" would obviate this rejection.

In the interest of compact prosecution, the claims (specifically, step (ii)) are interpreted as being drawn to "transplanting the β cell of step (i)".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Hunger et al. (European Journal of Immunology, 1997; Vol. 27, pages 255-261).

Hunger teaches a transgenic mouse wherein all of the pancreatic β cells of the mouse comprise a nucleic acid that encodes and expresses a soluble type I tumor necrosis factor (TNF) alpha receptor that binds to TNF-alpha and inhibits TNF-alpha signaling in the cell (e.g., see abstract; p. 255; p. 257). Therefore, the soluble type I TNF-alpha receptor is a dominant negative TNF-alpha receptor. It is noted that the instant claims are not explicitly drawn to a transgenic animal cell; however, given the broadest reasonable interpretation, the claim (i.e. a mammalian β cell comprising a recombinant nucleic acid molecule encoding and expressing a soluble type I TNF alpha receptor decoy protein) reads on a transgenic mouse pancreatic β cell that comprises a recombinant nucleic acid molecule that encodes and expresses the soluble TNF-alpha receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muruve et al. (Transplantation, 1997; Vol. 64, pages 542-546) in view of Hunger et al. (European Journal of Immunology, 1997; Vol. 27, pages 255-261).

The instant claims are drawn to methods comprising introducing into a β cell a nucleic acid molecule encoding a soluble type I TNF alpha receptor decoy protein and transplanting the β cell into an individual to reduce β cell dysfunction (claim 31), including β cell apoptosis (claim 35).

Muruve teaches that an adenoviral vector can be used to express a gene of interest in a pancreatic β cell for an extended period of time (e.g., see abstract, p. 542; p. 545, last two paragraphs). Furthermore Muruve teaches that the pancreatic β cell comprising the adenoviral vector can be transplanted into an individual such that the transplanted β cell expresses the gene of interest encoded by the adenoviral vector expresses said gene of interest for an extended period of time. As such, Muruve teaches an adenoviral vector that can be used for ex vivo gene therapy to express a therapeutic gene of interest in a pancreatic β cell.

Muruve does not teach that the adenoviral vector can be used to deliver and express a soluble TNF-alpha receptor dominant negative protein.

However, Hunger teaches that expressing a soluble TNF-alpha dominant negative receptor protein in mouse pancreatic β cells reduces β cell dysfunction that results in diabetes (including β cell apoptosis) compared to β cells that do not express the soluble TNF-alpha receptor protein.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Muruve such that the adenoviral vector expressed the a soluble TNF-alpha dominant negative receptor protein to make the claimed invention with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modification because (1) Muruve teaches, "using the replication deficient adenovirus, it is possible to express foreign proteins in pancreatic islets for extended periods of time without effecting their function in glucose homeostasis" (See p. 545, last paragraph), and (2) Hunger teaches that expressing soluble TNF-alpha receptor dominant negative protein in a β cell, "results in the complete

protection... against a variety of in vivo pathological conditions mediated by TNF release... [β cells] bearing this transgene fail to develop diabetes..." (See p 255, last paragraph).

Claims 31 and 35 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Muruve et al. (Transplantation, 1997; Vol. 64, pages 542-546) in view of Hunger et al. (European Journal of Immunology, 1997; Vol. 27, pages 255-261) and further in view of any of the following: Petrik et al. (Endocrinology, 1998; cited in the specification), Russell et al. (Journal of Neurobiol. 1998; cited in the specification), Symons et al. (PNAS, 1995; cited in the specification) or LaCasse et al. (Oncogene, 1998; cited in the specification).

The instant claims are drawn to methods comprising introducing into a β cell a nucleic acid molecule encoding a soluble type I TNF alpha receptor decoy protein as well as a nucleic acid encoding any of the following; NF-AT, STAT-6, IRAP, IGF-I and IGF-II and transplanting the β cell into an individual to reduce β cell dysfunction (claim 31), including β cell apoptosis (claim 35). It is noted that claims 31, 35 and 39 encompass a markush group of anti-apoptotic molecules that were known perform the same general function, inhibiting apoptosis (e.g., see indicated references).

Muruve and Hunger together suggest methods comprising introducing into a β cell a nucleic acid molecule encoding an inhibitor of apoptosis, and specifically teaches using a soluble type I TNF alpha receptor decoy protein as the anti-apoptotic molecule and transplanting the β cell into an individual to reduce β cell dysfunction as indicated in the above rejection.

Muruve and Hunger do not teach that the anti-apoptotic molecule can be any of IGF-I, IGF-II, NF-AT, STAT-6 or IL-1ra(IRAP).

However, it was well recognized in the art that IGF-I, IGF-II, NF-AT, STAT-6 or IL-1ra(IRAP) are inhibitors of apoptosis (i.e., they were recognized as antiapoptotic molecules and could be used in methods of inhibiting apoptosis, as acknowledged in the specification).

Specifically, Petrik et al. (Endocrinology, 1998; cited in the specification on page 7, first full paragraph) teaches that IGF-II is an inhibitor of apoptosis; Russell et al. (Journal of Neurobiol. 1998; cited in the specification see the paragraph bridging pages 6-7) teaches that IGF-I is an inhibitor of apoptosis, Symons et al. (PNAS, 1995; cited in the specification on page 5, second paragraph) teaches that IRAP (IL-1 Ra) is an inhibitor of apoptosis, and LaCasse et al. (Oncogene, 1998; cited in the specification see the paragraph bridging pages 15-16) teaches that NF-AT and STAT6 are an inhibitors of apoptosis.

Since NF-AT, STAT-6, IRAP, IGF-I and IGF-II were recognized in the art as apoptosis inhibitors (see the indicated references cited in the specification), it would have been prima facie obvious to one of skill in the art at the time of filing to combine the teachings of Muruve and Hunger with any of Petrik et al., Russell et al., Symons et al. or LaCasse et al. to make the claimed invention with a reasonable expectation of success. The motivation is provided by Muruve who teaches the general principle that apoptosis inhibitors can be used as gene therapeutic agents.

Response to Arguments

Applicants' arguments with respect to the previously set forth rejection of claims under 35 USC 112, 2nd paragraph (see pp. 6-7 of the response filed 10/7/04) are persuasive. Therefore, the previous rejection is withdrawn. However, a new grounds of rejection is set forth for the reasons indicated herein.

Applicants' arguments with respect to the previously set forth rejection of claims under 35 USC 112, 1st paragraph (see pp. 7-10 of the response filed 10/7/04) are persuasive. Therefore, the previous rejection is withdrawn.

Applicants' arguments with respect to the previously set forth rejection of claims under 35 USC 102 (see pp. 10-11 of the response filed 10/7/04) are persuasive. Therefore, the previous rejection is withdrawn. However, a new grounds of rejection is set forth for the reasons indicated herein.

Furthermore, a new rejection of claims under 35 USC 103 has been set forth for the reasons indicated herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art unit 1635

DAVE TRONG NGUYEN
PRIMARY EXAMINER